Precision medicine in psoriatic arthritis: How should we select targeted therapies?

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Psoriatic arthritis (PsA) is a heterogeneous inflammatory arthritis associated with psoriasis. Patients manifest variable presentations with potential involvement of peripheral joints, spine, tendons, skin and nails. In recent years there has been a rapid expansion in targeted treatment options for the condition but typically less than half of patients receiving therapy achieve an optimal treatment target. Many patients respond to second or third line biologic therapies, but we have little evidence to guide choice of therapeutics for the individual. At present, choice of therapy is driven by limited clinical phenotype, clinician familiarity and cost.

Here we review recent data that have highlighted the potential for personalised, or precision medicine in PsA and other forms of inflammatory arthritis, but this is still at a preliminary stage. In the future a combination of detailed immunophenotyping and sophisticated statistical analysis should be able to facilitate a personalised medicine approach in PsA following examples from other clinical areas such as oncology. This change in approach to the treatment of PsA has the potential to maximise outcomes for patients, providing optimal therapies without delay.

Psoriatic arthritis (PsA) comprises part of an inflammatory syndrome that occurs in 15-30% of people with psoriasis [1]. It is a highly heterogeneous condition with diverse musculoskeletal and extra-articular manifestations. Although in recent years, there has been a rapid increase in the number of therapeutic options in PsA, there is a lack of evidence to guide a precision approach to therapy selection for individuals.

In general, the treatment of PsA has followed a reactive 'step-up' 'trial and error' approach using different conventional disease-modifying anti-rheumatic drugs (DMARDs) followed by biologic DMARDs if patients fail to adequately respond [1,2]. This practice has been challenged recently with new recommendations published in 2018 from the American College of Rheumatology and the National Psoriasis Foundation which recommended the use of biologic DMARDs first line[3]. However, PsA is very variable in terms of both presentation and prognosis. Internationally, approximately 50% of patients require biologic therapy or targeted synthetic DMARDs, most commonly after failure of conventional synthetic DMARDs [4]. The therapies currently available beyond conventional synthetic DMARDs for PsA are directed at five key targets. The first, and most established therapies are tumour necrosis factor inhibitors (TNFi) - monoclonal antibodies or receptor antagonists blocking the action of TNF, a key predominantly myeloid-derived cytokine involved in multiple immune cell mediated effector pathways. Two further classes of biologic therapies are licensed for PsA: Interleukin (IL-) 17A inhibitors - monoclonal antibodies targeting the cytokine IL-17A that plays a pleotropic role in inflammation including recruitment of neutrophils and stromal cell activation[5]; and IL-12/-23 inhibitors – monoclonal antibodies neutralising either the shared subunit (p40) of both IL-12 and IL-23 cytokines or the p19 subunit of IL-23, working upstream of both the IL-17A and T-helper 1 (Th1) pathways[6]. In addition to the biologic therapies, two oral small molecule agents are now available: Janus Kinase (JAK) inhibitors – small molecule drugs blocking signal transduction downstream of multiple cytokine receptors; and apremilast, a phosphodiesterase 4 (PDE-4) inhibitor – small molecule drug blocking the degradation of cyclic-AMP in immune cells and thereby altering inflammatory cytokine expression in a range of leukocyte subsets.

Whilst the expansion in different therapeutic options is welcome, it raises new questions about how to guide therapeutic choice in PsA. When considering treatment response, it is increasingly recognised that to optimise quality of life and functional ability, treatment should be focused on achieving a treatment target. Such a target should encompass the different domains of psoriatic disease to ensure good disease control. The minimal disease activity (MDA) criteria has been recommended as the treatment target in PsA as there is evidence that patients who achieve the MDA criteria have less joint damage, as measured using x-rays, better quality of life and function[7]. However, the current approach of simply using biologics in patients with PsA without personalisation or stratification to particular therapies results in over 50% of patients failing to achieve the therapeutic target of treatment defined by the MDA criteria, although other external factors are also likely to be implicated [7,8].

We know that some people who fail to respond to a first line biologic will have a good response when they switch to a drug with a different mechanism of action[9] suggesting that individuals' disease pathogenesis may be distinct, or that different pathways can dominate over time. Moreover, some patients will also respond to a switch within the same therapeutic class. We know very little about the impact of the first, second or third chosen therapies on the stability or evolution of pathobiology over time, and how the sequencing of different agents can influence this.

In routine clinical practice, biologics and targeted synthetics drugs are usually continued for a minimum of 12-24 weeks before response can be fully evaluated[1,2] with MDA assessed later in that time period[10]. As we cannot currently predict who will respond to a given therapy this means a long delay on a therapy that may never work if they are the recipient of an ineffective therapeutic. The resulting delays incurred on ineffective and potentially toxic therapy are associated with negative outcomes with regard to patients' quality of life, future well-being and a higher cost burden to healthcare systems. This review focuses on the current evidence around personalised selection of

biological and small molecule targeted therapies in PsA, which is one of the key unmet needs in treatment strategy.

Search strategy and selection criteria

This review is based on a narrative rather than systematic literature search. Searches were performed in Medline to identify English language papers focused on treatment and stratification of therapies in psoriatic arthritis published before 31st March 2019. Key abstracts were identified from the European League Against Rheumatism and American College of Rheumatology Annual Meetings in 2016-2018.

Current strategy

In routine clinical practice, clinicians select biologics and targeted synthetic DMARDs for patients with resistant active PsA based on a limited clinical phenotype. For instance, when choosing therapy for PsA, choices are generally focused on the treatment of musculoskeletal (arthritis, enthesitis, axial disease and dactylitis) and dermatological (psoriasis) manifestations. In rheumatology, the majority of drug trials in PsA to date have predominantly recruited patients with polyarthritis and focused on peripheral arthritis as the primary outcome. Response rates for most of these studies are largely similar with around 50-60% of patients achieving the American College of Rheumatology (ACR) 20% improvement response criteria (ACR20) outcome. Over the last two decades, there has been an increasing recognition of the importance of musculoskeletal manifestations beyond the joints, namely enthesitis, dactylitis and spondylitis but these are commonly only assessed as key secondary outcomes rather than in specific studies powered to specifically address these aspects of disease. Similar responses are seen with most of these therapies for peripheral psoriatic arthritis and few current head-to-head data exist in PsA. Whereas international treatment recommendations support the use of those therapies with proven efficacy, they remain by necessity ambivalent in recommending one particular drug over another [11]. In comparison, there have been a number of

head-to-head studies in psoriasis that have differentiated response to therapy, which may help guide the selection of optimal treatment, for the skin at least.

Beyond musculoskeletal and skin manifestations, extra-articular manifestations and comorbidities may also be particularly relevant in selection of biologic or targeted synthetic DMARDs given differential efficacy and safety profiles. In current clinical practice, most patients with PsA receive TNF inhibitors as first line biologic, presumably due to longer term outcome data, physician familiarity and lower costs when using TNF biosimilars.

The lack of data assisting choice of biologics is frustrating for both clinicians and patients who want to know which therapy would be best for them. The James Lind Alliance (a not-for-profit government-funded UK organisation) supervise priority setting partnerships (PSPs) to collate unmet needs identified by patients, carers and clinicians and then prioritise these creating a "top ten" list. Unfortunately, there has not been a James Lind PSP for PsA however, in the 2018 Psoriasis PSP, the question "What factors predict how well psoriasis will respond to a treatment?" was ranked 3rd in the top ten unmet needs, after "Do lifestyle factors such as diet, dietary supplements, alcohol, smoking, weight loss and exercise play a part in treating psoriasis?" and "Does treating psoriasis early (or proactively) reduce the severity of the disease, make it more likely to go into remission, or stop other health conditions developing?". This highlights the importance that both patients and clinicians ascribe to the issue of predicting therapeutic response.

Comparison of different targeted therapies

Direct head to head studies will be the gold standard in evaluating the preferred hierarchy of therapeutic choice in PsA. In recent phase III studies, the use of an adalimumab internal control has been utilised alongside IL-17A[12] and JAK inhibitors[13] supporting the impression that response rates are similar, although these studies are not powered for a head-to-head comparison between active treatment arms. To date, there is only one large head-to-head study comparing different biologics in PsA which compared ixekizumab (IL-17A inhibitor) with adalimumab (TNF inhibitor). The study,

presented in abstract form in 2019 has shown a superiority of ixekizumab in the primary outcome (a combined outcome of patients achieving both ACR50 and PASI100) compared to adalimumab, which was expected given the previously proven superior results of IL-17A inhibitors in psoriasis response (PASI100). Using ACR50 alone, non-inferiority for ixekizumab compared to adalimumab was confirmed[14]. In additional key secondary outcomes, superiority for ixekizumab was confirmed for a number of composite disease activity measures (including the minimal disease activity criteria and PsA disease activity score- PASDAS) and enthesitis resolution.[14] Unfortunately, the data available so far do not yet advance our decision-making algorithm in PsA, and we must await further analysis, such as the differences in domains within the composite measures which will be informative once this study is fully published.

In PsA trials, psoriasis has typically been assessed as a secondary outcome measure. In dermatology however, head-to-head studies have been more common for pure chronic plaque psoriasis and demonstrated clear differential efficacy in psoriasis. Ustekinumab (p40 inhibitor) is superior to TNF inhibitors (at least in the form of etanercept)[15], while IL-17A[16-19] and IL-23 p19 inhibitors in turn [20,21] are both superior to TNF inhibitors and ustekinumab. The superiority of ustekinumab over TNF inhibitors is not surprising given the strong genetic association of *IL23R* polymorphism with psoriasis and extensive evidence suggesting a central role for the IL-23/IL-17 axis in psoriasis pathogenesis. The differential clinical response between ustekinumab and IL-17A inhibitors is more intriguing, as several studies have highlighted the role of IL-23-independent IL-17A or IL-17F production by innate-type T cells such gamma-delta T cells which are found in the skin[22-24]. However, this does not account for the differential clinical response observed between ustekinumab (IL-12/IL-23 p40 subunit inhibitor) and the IL-23 p19 subunit inhibitors. One particular murine study showed a protective role for IL-12 in a model of psoriasis by limiting the recruitment of IL-17 producing-gamma-delta T cells and further showed a direct role for IL-12 in maintaining an inflammatory keratinocyte transcriptional programme [25]. These data would suggest that targeting both the protective IL-12 response and the pathogenic IL-23 response by ustekinumab could be less efficacious than the

selective targeting of IL-23. Whilst this evidence for psoriasis and nail involvement contributes to treatment guidance in PsA, it should be remembered that skin psoriasis in PsA may be different, and often less severe, than that in psoriasis patients recruited to phase III studies.

Considering enthesitis in PsA, there has been one small head-to-head study namely the Enthesitis Clearance in PsA or ECLIPSA study. This study included only 47 patients randomised to either open label TNF inhibitors or ustekinumab, but met its primary endpoint with complete clearance of enthesitis on the SPARCC score at 24 weeks achieved by 74% of ustekinumab treated patients vs 42% of TNF inhibitor treated patients (p=0.018). It is important as it included all patients with active enthesitis, regardless of joint counts, thus including a mix of oligo and polyarthritis patients. It confirmed similar arthritis responses between the drugs and a superior skin clearance with ustekinumab. This translated into a trend towards higher achievement of the minimal disease activity (MDA) treatment target with ustekinumab (77% vs 45%) when peripheral arthritis, skin and enthesitis are assessed together,[26] similar to the superior composite responses seen in the ixekizumab head-to-head study discussed above.

The response to different targeted therapies may not be consistent across peripheral musculoskeletal tissues such as arthritis and enthesitis, as seen above. This is also true when considering axial disease in PsA, highlighting potential pathogenic differences between peripheral and axial disease (reported in 20-50% of patients with PsA). The results of phase III studies in ankylosing spondylitis (AS), the prototypic axial inflammatory disease, have thrown up some intriguing results. While both TNF inhibitors and IL-17A inhibitors[27] were effective, and are now widely used in clinical practice for AS, this was not the case with other pathways listed above. Both ustekinumab and risankizumab, an IL-23 p19 inhibitor, failed to achieve the primary end-point in their initial trials in AS [28,29] and therefore the development programmes for both were halted. Similarly the PDE-4 inhibitor, apremilast did not meet the primary outcome in the POSTURE trial halting development[30]. The IL-12/-23 results were perhaps surprising given the established genetic

association between *IL23R* polymorphism and AS[31]. At best we have not yet properly understood the mechanistic interpretation of the genetic associations and the specific single nucleotide polymorphisms contained therein. In future, a formal evaluation of the functional prediction of a given polymorphism prior to assumption of pathogenetic association would seem prudent. It has also been suggested that perhaps IL-23-independent IL-17A production may be crucial in the observed divergent therapeutic response to two drugs targeting the same pathway though the evidence here is sparse[32,33]. Furthermore, pharmacodynamics and tissue drug penetration remain theoretical challenges or as yet misunderstood pathologic events in axial disease.

More recently, data from the human B27-transgenic rat model of AS have suggested that neutralisation of IL-23 protects against onset of the disease but fails to control established disease, suggesting that disease pathologic kinetics may be important[34]. One reason may be that other pro-inflammatory pathways, including upregulation of GM-CSF by T cells [25] and innate lymphoid cells [35], may also drive the pathogenic response in established disease. Interestingly, GM-CSF may be a crucial factor in the tissue-specific responses observed between skin and joints. While a role for GM-CSF has been shown in peripheral and axial arthritis [36,37], inhibition of this cytokine in a phase II study of psoriasis failed to show efficacy [38] in contrast to positive outcomes in RA[39]. Interestingly, genome-wide association studies demonstrate a region of association around the GM-CSF gene (*CSF2*) in PsA but not skin psoriasis [40]. Taken together, it would seem that pathogenic cell type, the timing of the therapeutic intervention, the specific site of inflammation and other activated inflammatory pathways are all crucial in the success of a therapeutic intervention across the psoriatic spectrum.

Evidence to date concerning pathogenesis-derived strategies

The pathogenesis of psoriasis and PsA is complex, involving numerous genetic risk loci, cell types and pathways. Currently, multiple lines of evidence focus on a key role for T cells as central drivers [41]. From the genetic perspective, the association with MHC class I polymorphisms confers the strongest genetic susceptibility [42,43]. Given the role of MHC class I molecules in activation of CD8+ T cells,

several groups have shown a clonal expansion of these cells at the inflammatory site and possible overlap of clones between skin and joints suggesting a potentially shared antigenic driver between skin and joints [44,45]. Intriguingly, IL-17A-producing CD8 T cells are expanded in inflamed PsA synovial fluid [46] and this observation may be a crucial link between the disease-associated *IL23R* locus, additional disease-associated loci that relate to the IL-17 pathway (*IL12B*, *IL23A*, *TRAF3IP2*) and the MHC[41]. A number of studies have shown that MHC class I loci can broadly be used to stratify patients into clinical phenotypes [47], but studies linking genetics to a therapeutic response are still lacking. As our understanding of the pathogenesis increases, we can work towards unravelling the key disease drivers by integrating the individual genetic profile with the upregulated inflammatory pathways at the individual patient level.

In principle, pathogenic information has been used to define therapeutic targets but not the subsequent strategy whereby such agents are then employed in the clinic. Thus, few data yet support the application of precision medicine principles in rheumatology in general, despite moves towards tissue-based therapy in other specialities like oncology. Outcomes obtained in pharmacogenomics have so far been generally disappointing. Epigenetic and transcriptional approaches in blood or target tissue offer some promise, as do proteomic and metabolomic considerations. For example, the precision choice of therapies has already begun to be addressed in rheumatoid arthritis (RA)[48]. In RA, differences in genomic architecture represented by a chromosome conformation signature (CCS) in baseline blood samples have been shown to be predictive markers of methotrexate response[48]. When considering response to biologics, the ORBIT trial compared two biologics in RA with different modes of action[49], confirming non-inferiority of rituximab (B-cell depleting therapy) compared to TNFi therapy. The study also investigated predictors of response to each drug with RNA-seq data from baseline peripheral blood samples, identifying two distinct 23 gene transcriptional signatures that could classify responders to TNF inhibitors and rituximab respectively[50]. Thus, in sero-positive RA, predictive molecular signatures may be present in baseline peripheral whole blood that can help identify future responsiveness to

TNFi and rituximab therapies. In addition to studies seeking a blood based predictive assay (the "liquid biopsy"), synovial tissue studies are likely to offer invaluable insights and potential therapeutic value to this type of prediction and are eagerly awaited[51,52].

Recently, the first study addressing precision medicine in PsA was published. This trial performed in Japan evaluated the use of baseline CD4+ T cell immunophenotype characteristics to select an appropriate therapy in PsA. The authors first defined peripheral blood Th1 and Th17 phenotypes based on CCR6 and CXCR3 expression on $CD4^+$ T cells and then measured co-expression of known T cell activation markers CD38 and HLA-DR[53]. They defined four groups based on the predetermined cut-offs for high and low levels of Th1 and Th17, based on quartiles in healthy controls. Interestingly, whilst the proportion of activated Th17 cells was found to be higher in PsA patients compared to healthy controls, the proportion of Th1 cells was not significantly different. Sixty-four PsA patients starting biologic therapy were then randomly divided into a standard care group and a precision medicine group based on this peripheral blood lymphocyte analysis (Figure 1)[53]. The precision medicine group had significantly higher rates of ACR20 response and low disease activity suggesting a possible benefit in favour of the precision medicine approach. However, the study was small, not powered to compare the groups, while not all outcomes, including psoriasis responses, were significantly different[53]. Nonetheless, this is the first study using baseline immunophenotype to select therapy in PsA and despite its limitations has shown some promising results.

The use of a phenotyping strategy based on CCR6 and CXCR3 expression is deliberately over-simplistic presumably chosen for pragmatic reasons – whilst these chemokine receptors are enriched on Th17 and Th1 cells respectively, they are not exclusive to these two subsets [54]. Other markers such as CD161 which are also enriched on Th17 cells [55] may allow for more accurate immunophenotyping. The restriction of the immunophenotype on $CD4^+$ T cells alone may miss other important cellular players in PsA pathobiology. In particular, an increasing role for other "type 17" immune cells including CD8+ T lymphocytes is now appreciated [46] which may explain the dominant

role of MHC class I polymorphisms in PsA heritability [56]. Other IL-17 producing cells, such as MAIT, γδ T cells or type 3 innate lymphoid cells (ILC3) may also play roles in an MHC class I-independent manner.

Even with more in-depth immunophenotyping, there are questions about which therapies should be given to particular subgroups of patients. One might argue that ustekinumab should be the therapy selected for the Th1/Th17 co-dominant group since this monoclonal removes a common subunit from both pathways, yet in the previous study this group was assigned to receive TNF blockade. Blockade of TNF was the first successful biologic strategy in PsA [57] based on the pleotropic pro-inflammatory effects of this predominately myeloid-derived cytokine [58]. The role of TNF in the balance of Th1 versus Th17 cells is not fully understood, however, with some groups reporting an increase the percentage of circulating Th17 cells after treatment with anti TNF [59,60].

Future research needed

Given these initial data, how should we move forward with personalised choice of targeted therapies in PsA? Given the significant clinical heterogeneity of the disease involving a range of tissues, large studies will be needed - it will be important to evaluate multiple clinical domains of the disease. We have already seen differential responses to targeted therapies in psoriasis and axial disease suggesting that different clinical phenotypes may also be used to guide therapeutic choices to reflect underlying tissue-specific differences. Given the likely diversity in pathogenesis, it seems plausible that more complex immunological approaches may yield better predictive accuracy. Crucially, a more detailed and systematic molecular and cellular phenotyping approach, using for example advanced techniques such as mass-cytometry (CyTOF) that allows simultaneous detection of up to 40 phenotypic markers at a single-cell resolution [61] may identify previously unknown inflammatory cell (pheno)types in disease pathogenesis. A recent study in RA using CyTOF defined a novel peripheral T-follicular helper-like cell-type which is able to support pathogenic auto-antibody

production [62]. The application of unbiased approaches such as next-generation sequencing in systemic lupus erythematosus and ANCA-associated vasculitis has also highlighted a number of key CD8+ T cell-related transcripts that define prognosis [63]. We predict that these approaches will not only allow better targeting of existing therapies, but will justify the use of these targeted therapies earlier in the disease course in those patients with a poorer prognosis.

With such diverse clinical phenotype and complex genetic and immunological assessments it is likely that newer statistical methodologies such as machine learning and artificial intelligence may be useful to combine potential predictors of response[64]. Algorithms such as deep neural networks can synthesise data from millions of inputs using combinations far more complex than humans could compute. This offers a distinct advantage in such a complex disease where diverse presentations, pathophysiology and comorbidities, as well as therapies with different mechanisms of action must be considered. It is also possible that subsequent comprehensive investigation of pathophysiological patterns identified using machine learning may further advance our understanding of the disease.

As new therapies become available, additional research will be required to investigate predictors of response to these drugs and to integrate this knowledge into a treatment strategy. Some of the newer therapies in development currently may also show subtle differences within a class of drug. For example, bimekizumab is an inhibitor of IL-17 that inhibits both IL-17A and IL-17F, unlike secukinumab and ixekizumab, which only inhibit IL-17A. To date, one JAK inhibitor, tofacitinib has been approved for PsA. A number of other JAK inhibitors are also in development, with slightly different JAK selectivity, potentially impacting on predictors of response. Thus, the range of predictive models to identify the optimal therapeutic approach are likely to become increasingly complex, but even more important, as increasing numbers of medications become approved.

Summary

The increasing number of targeted therapies brings new challenges and opportunities to improve care for patients with PsA. At present, choice of therapy is driven by limited clinical phenotype, clinician familiarity and cost. However, early evidence provides proof-of-the concept molecular and cellular precision medicine approaches may be possible in inflammatory arthritis and specifically in PsA. Further research combining large clinical cohorts, detailed immunophenotyping and sophisticated statistical methodology should provide insight into a precision approach to the selection of targeted therapies. Such an approach in precision medicine, combined with advancements in overarching treatment strategy has the ability to revolutionise the treatment approach in PsA, improving outcomes for patients and minimising the cost from ineffective therapies.

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Conflicts of Interest

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Author contributions

Laura Coates and Hussein Al-Mossawi wrote the first draft of this manuscript. All authors reviewed and revised the text and gave final approval to submit.

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Text Box 1 – Targeted therapies currently available for psoriatic arthritis

Biologic therapies	Tumour necrosis factor inhibitors (TNFi) Blockade of TNF, a key predominantly myeloid-derived cytokine involved in multiple immune cell mediated effector pathways.
	Interleukin (IL-) 17A inhibitors Blockade of IL-17A, a cytokine that plays a pleotropic role in inflammation including recruitment of neutrophils and stromal cell activation[5]
	IL-12/-23 inhibitors Blockade of either the shared subunit (p40) of both IL-12 and IL-23 cytokines or the p19 subunit of IL-23, working upstream of both the IL-17A and T-helper 1 (Th1) pathways[6]
Oral small molecules	Janus Kinase (JAK) inhibitors Blockade of signal transduction downstream of multiple cytokine receptors
	Apremilast, a phosphodiesterase 4 (PDE-4) inhibitor Blockade of the degradation of cyclic-AMP in immune cells and subsequent modulation of cytokine production by a range of leukocytes

Figure 1 - Cellular source and tissue-specific inflammatory role of cytokines in PsA

Legend body: Proposed model highlighting the key role of T-cell and myeloid cytokines in driving PsA inflammation at different anatomical sites. IL-17A and TNF have been clinically proven to suppress inflammation in the axial spine, peripheral joints and skin. IL-23 blockers have shown clinical efficacy in the skin and peripheral joints but not in axial inflammation. GM-CSF blockade is currently being trialled for axial and peripheral joint inflammation but trials for skin inflammation have failed to show efficacy.